

**REMARKS**

Applicants have studied the Office Action of January 15, 2003 ("Office Action"), and have amended the Specification and claims in response thereto. Applicants thank Examiner for withdrawing the Restriction Requirement of September 19, 2002 in its entirety, and for thereby subjecting all claims to substantive examination. It is respectfully submitted that the application, as amended, is in condition for allowance. Claims 1-5 and 8-42 are pending in the present application. Claims 10-12, 27-29 and 37 have been amended, and claims 6 and 7 have been cancelled. No new matter has been added. Reconsideration and allowance of the claims in view of the foregoing amendment and the ensuing remarks are respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims and Specification by the current Amendment. The attachment is captioned "Version with Markings to Show Changes Made."

The Specification has been amended to correct typographical errors included therein at page 2, line 10, and at page 14, line 2.

Claims 10-12 and 27-29 have been amended to correct claim dependency. As amended, claims 10-12 depend from claim 5, and, as amended, claims 27-29 depend from independent claim 21.

Claim 37 has been amended to more particularly describe that which Applicants consider to be their invention. Claim 37, as amended, describes "*an isolated stem cell that does not express  $\beta_2$ -microglobulin,*" which is isolated by the process of "*obtaining a sample of cells from a mammal; sorting, from the sample, cells that express  $\beta_2$ -microglobulin from cells that do not express  $\beta_2$ -microglobulin; and selecting the isolated stem cell from the sample of cells that do not express  $\beta_2$ -microglobulin.*" Support for this amendment may be found throughout the Specification; for example, at page 6, lines 20-23.

In the Office Action, Examiner objected to the drawings because the top margins of Figs. 1-4 were insufficient and because the various views depicted therein were "*not labeled separately or properly,*" as noted in the Notice of Draftsperson's Patent Drawing

Review. Regarding the objection to the labeling of Figs. 1-4, this objection is respectfully traversed.

Applicants enclose herewith a set of revised drawings including corrected margins. No substantive alterations have been made to the drawings, other than the adjustment of the margins.

Additionally, several of these drawings include color photographs. A Petition to accept these color photographs into the application was earlier filed and subsequently accepted, per the notice included with the Office Action. In order to correct the margins in the color photographs, Applicants submit herewith three (3) copies of each of Figures 1, 2 and 4 -- the figures including color photographs that were described in the Petition.

Applicants are unclear as to the draftsman's objection to Figs. 1-4 based upon the labeling thereof, as Applicants believe that the labeling of the individual views depicted are entirely proper, and comply in all respects with the requirements of 37 CFR 1.84(h)(2). As such, Applicants respectfully request that Examiner reconsider and withdraw this objection to Figs. 1-4.

In the Office Action, Examiner rejected claims 1-36 under 35 U.S.C. § 112, first paragraph, asserting that *"the specification does not enable any person skilled in the art...to make and/or use the invention commensurate in scope with these claims."* Examiner found that the Specification indicates, *"cells such as spermatozoa do not express  $\beta_2m$ ,"* and thereby concluded that *"obtaining a sample of cells...and sorting  $\beta_2m^-$  cells from  $\beta_2m^+$  cells and further selecting stem cells from the  $\beta_2m^-$  cell population, would not necessarily result in the isolation of stem cells, as the 'sample of cells'...could contain other cells that would not be stem cells, for example, spermatozoa."* With respect to claims 6 and 7, which have been cancelled by virtue of the present amendment, Applicants respectfully submit that this rejection is moot. With respect to the remaining claims, however, this rejection is respectfully traversed.

A claim is enabled so long as an individual of reasonable skill in the art *"...could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation"* (emphasis added). *United States v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); MPEP § 2164.01. Moreover, "as

*long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied" (emphasis added). In re Fisher, 427 F.2d 833, 839 (CCPA 1970); MPEP § 2164.01(b).*

The methods of Applicants' invention (as set forth in independent claims 1 and 21), include three components: (1) obtaining a sample of cells from a mammal; (2) sorting these cells based on  $\beta_2m$  expression; and (3) selecting/sorting stem cells from the  $\beta_2m^-$  population of the cells. Each of these components of Applicants' invention is described in detail throughout the Specification, and various Examples included in the Specification provide sample methods for making and using the invention. In particular, the second component (i.e., sorting cells based on  $\beta_2m$  expression) may be performed by way of fluorescent activated cell sorting (FACS) or magnetic bead cell sorting (MACS) -- both of which are methods well known to those of skill in the art. Still further, the Specification describes a double magnetic bead cell sorting (D/MACS) process that the inventors developed, and which may be used to sort the sample of cells described in the invention. Specific instructions as to how the D/MACS procedure may be executed are included at page 14, line 10 through page 15, line 12.

The Specification provides numerous examples of ways in which one may perform the methods of the claimed invention; particularly described across ten pages of Examples. One of reasonable skill in this highly specialized field of art would have no difficulty discerning at least one means for carrying out the methods of the invention based on the Specification and information generally known in the art, and no undue experimentation would be required to do so. Applicants have thus not merely met, but have exceeded the requirements of 35 U.S.C. § 112, first paragraph, with regard to enabling the claims.

With respect to Examiner's assertion that cells other than stem cells (e.g., spermatozoa) may be included in the cells isolated by the methods of the invention, Applicants respectfully note that the standard for enablement does not require that one seeking to isolate stem cells must not have to conduct experiments to do so. Experimentation is permissible. Even "*a considerable amount of experimentation is permissible, if it is merely routine.*" In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988);

MPEP § 2164.01. In Teletronics, for example, competitors had to experiment for 6 to 12 months, call upon four different specialists (an electrical engineer, a surgeon, a biomechanic and a biologist), and spend \$50,000 to determine how to practice the invention at issue; yet even this amount of experimentation was not undue, because the steps required to carry it out were routine. The same principal applies in the present application. Those of ordinary skill in the art will have to execute no more than routine steps to remove spermatozoa or similar cells from a sample of stem cells obtained with the methods of the present invention.

In light of the foregoing remarks, Applicants respectfully submit that claims 1 and 21, as well as claims 2-5, 8-20 and 22-36 that depend therefrom, are sufficiently enabled by the Specification. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Examiner rejected claims 1-20, 27 and 29 under 35 U.S.C. § 112, second paragraph, as being indefinite. Examiner found that claim 1 is *"incomplete"* because *"it is unclear how the stem cells are 'selected' from a sample of cells, as the metes and bounds of the term 'selected' are not specifically defined."* Examiner further found that claim 6 is *"unclear,"* because although it describes *"isolating pluripotent stem cells...the claim does not provide specific steps in order to show that such selection would result in pluripotent stem cells."* Examiner further found that claim 7 is *"unclear,"* because although it describes *"selecting embryonal stem cells...the claim does not provide specific steps to show that selection would result in embryonal stem cells."* Examiner further found that claims 10 and 27 are *"unclear,"* because *"the claim recites that the MHC marker of claim 8 or claim 25, respectively, is Thy-1...[but] Thy-1 is not a MHC antigen."* Finally, Examiner found that claims 11 and 29 are *"unclear,"* because *"the claim recites that the MHC marker of claim 8 or 25, respectively, is a marker consisting of flt-3, CD34, c-kit, CD38...[but] these markers are not MHC markers."* With respect to claims 6 and 7, which have been cancelled by virtue of the present amendment, Applicants respectfully submit that this rejection is moot. With respect to the remaining claims, however, this rejection is respectfully traversed.

In analyzing a claim with regard to definiteness, an Examiner “*should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness*” (emphasis in original). MPEP § 2173.02. Moreover, “*in reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope*” (emphasis added). *Id.* The threshold for satisfying the requirement of definiteness is simply “*whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity*” (emphasis added). *Id.*

In Applicants’ claim 1, the method includes “*selecting stem cells from the sample of cells that do not express  $\beta_2$ -microglobulin.*” The term “selecting” is defined throughout Applicants’ Specification. In particular, Specification teaches the following:

*One identifies stem cells according to the method of the invention by first sorting, from a population of cells, cells that are  $\beta_2m^-$  from cells that are  $\beta_2m^+$ . One then selects from the  $\beta_2m^-$  cells the stem cell of interest; this is performed by sorting cells by their expression of a known cell marker. Any marker that is known to be associated with stem cells may be used. (emphasis added). Specification (page 6, lines 20-24).*

Selecting, as defined in Applicants’ Specification and as used in the claims thus has a specific meaning -- one uses selects stem cells of interest based on their expression of a particular surface marker. One of ordinary skill in this field of art would readily understand, based on Applicants’ disclosure, the metes and bounds of the term “selecting,” and would be capable of using conventional methodologies well-known to those possessing such skill to execute this aspect of Applicants’ claimed method. The threshold for definiteness is only a “*reasonable degree of particularity and distinctness*,” which Applicants have achieved with their use of the term “selecting,” as defined in the Specification.

As amended, claims 10 and 27 depend from claims 5 and 21, respectively, and no longer include the limitation that the stem cell markers that they describe are proteins “*expressed by one or more genes encoding the major histocompatibility complex.*” As such, it is believed that these claims are sufficiently clear, per the requirements of 35 U.S.C. § 112, second paragraph.

Applicants presume that Examiner's rejection of claim 11 was actually intended to be directed at claim 12, since claim 11 describes the markers RT1A, RT1B and RT1D, while claim 12 describes the markers flt-3, CD34, c-Kit and CD38 -- the latter being described in the text of the rejection. As amended, claims 12 (as well as claim 11) and 29 depend from claims 5 and 21, respectively, and no longer include the limitation that the stem cell markers that they describe are proteins "*expressed by one or more genes encoding the major histocompatibility complex.*" As such, it is believed that these claims are sufficiently clear, per the requirements of 35 U.S.C. § 112, second paragraph.

In light of the foregoing remarks, Applicants respectfully submit that claims 1-5, 8-20, 27 and 29 are not indefinite. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Examiner rejected claims 37-42 under 35 U.S.C. § 102(b) as being anticipated by Tsukamoto et al. (U.S. Pat. No. 5,643,741; "Tsukamoto"). In particular, Examiner indicated that "*the properties of the claimed stem cells are inherent properties of the stem cells,*" and that "*if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.*" This rejection is respectfully traversed.

To be anticipated, each and every element set forth in a claim must be found in a single prior art reference. MPEP § 2131; See, e.g., Verdegaal Bros. v. Union Oil Co. of Calif., 814 F.2d 628, 631. Tsukamoto describes a method for identifying the presence of stem cells by examining expression of particular cell surface markers. However, the claims of Applicants' invention, as amended, describe "*an isolated stem cell that does not express  $\beta_2$ -microglobulin*" (claim 37), wherein the isolated stem cell is obtained by the three-component process described above; namely: (1) obtaining a sample of cells from a mammal; (2) sorting these cells based on  $\beta_2m$  expression; and (3) selecting/sorting stem cells from the  $\beta_2m^-$  population of the cells. Tsukamoto does not teach, disclose or suggest the use of any such process. In particular, nowhere does Tsukamoto suggest the sorting of a sample of cells based on  $\beta_2m$  expression.

Tsukamoto, therefore, does not describe each and every element of Applicants' claims, and can not anticipate Applicants' invention.

In light of the foregoing remarks, Applicants respectfully submit that amended claim 37, as well as claims 38-42 that depend therefrom, are not anticipated by Tsukamoto. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b).

Examiner rejected claims 37, 41 and 42 under 35 U.S.C. § 102(b) as being anticipated by Thomson et al. (Science 1998, 282:1145-1147; "Thomson"). Specifically, Examiner noted that "*Thomson teach[es] pluripotent human embryonic stem cell lines which were derived from human blastocytes,*" and that "*the lack of expression of  $\beta_2m$  is an inherent quality of stem cells.*" This rejection is respectfully traversed.

Thomson describes pluripotent stem cell lines that exclusively characterize primate embryonic stem cells. However, the claims of Applicants' invention, as amended, describe "*an isolated stem cell that does not express  $\beta_2$ -microglobulin*" (claim 37), wherein the isolated stem cell is obtained by the three-component process described above. Thomson does not teach, disclose or suggest the use of any such process. In particular, nowhere does Thomson suggest the sorting of a sample of cells based on  $\beta_2m$  expression. Thomson, therefore, does not describe each and every element of Applicants' claims, and can not anticipate Applicants' invention.

In light of the foregoing remarks, Applicants respectfully submit that claims 37, as well as claims 41 and 42 that depend therefrom, are not anticipated by Thomson. Thus, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b).

The present application has been assigned to Cedars-Sinai Medical Center, by virtue of the Assignment recorded in the present application at Reel 012851, Frame 1549. Cedars-Sinai Medical Center is entitled to small entity status, per 37 CFR 1.27. Therefore, **small entity status is hereby claim d.** MPEP § 509.03.

For the foregoing reasons, the Applicants believe that the application is condition for allowance, and respectfully request early, favorable action on the merits. If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 488-7100 to discuss the steps necessary for placing the application in condition for allowance should the Examiner believe that such a telephone conference would advance prosecution of the application.

Respectfully submitted,

PILLSBURY WINTHROP LLP

Date: June 13, 2003

By: \_\_\_\_\_

  
Seth D. Levy  
Registration No. 44,869  
Attorney for Applicants

725 South Figueroa Street  
Suite 2800  
Los Angeles, CA 90017  
(213) 488-7100

Enclosure: Revised Formal Drawings  
Three (3) sets of color copies of Figures 1, 2 and 4 with corrected margins



**APPENDIX**

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE DRAWINGS:**

The drawings have been replaced by the enclosed drawings in which the margins have been corrected.

**IN THE SPECIFICATION:**

At page 2, line 4, the first full paragraph on that page is amended as follows:

This description of hematopoiesis is vastly incomplete, of course: biology has yet to determine a complete lineage for all the cells of the blood (e.g., it is has yet to identify all the precursor cells between the myeloid stem cell and the progenitor cells to which it gives rise), and it has yet to determine precisely how or why the myeloid cell differentiates into progenitor cells. Even so, hematopoiesis is particularly well studied; even less is known of the development of other organ systems. With respect to the brain and its development, for example, U.S. Patent No. 6,040,180 [6.040,180], the disclosure of which is hereby incorporated by reference, describes the "current lack of understanding of histogenesis during brain development." U.S. Patent No. 5,849,553, the disclosure of which is hereby also incorporated by reference, describes the "uncertainty in the art concerning the development potential of neural crest cells."

At page 14, line 2, the first full paragraph on that page is amended as follows:

Any population of cells where stem [stems] cells are suspected of being found may be sorted according to the method of the invention. Preferably, cells are obtained from the bone marrow of a non-fetal animal, and most preferably from a human. Fetal cells may also be used; the method of the invention may be used, for example, to obtain from such cells fetal neuronal stem cells. U.S. Patent Nos. 6,204,053 B1 and 5,824,489, the disclosures of which are hereby incorporated by reference, identify additional sources of cells that contain or are thought to contain stem cells; any of these cells may be sorted according to the method of the invention.

**IN THE CLAIMS:**

Claims 10-12, 27-29 and 37 are amended as follows:

10. (Amended) The method of claim 5 [8], wherein the marker is Thy-1.
11. (Amended) The method of claim 5 [8], wherein the marker is selected from the group consisting of RT1A, RT1B, and RT1D.
12. (Amended) The method of claim 5 [8], wherein the marker is selected from the group consisting of flt-3, CD 34, c-Kit, and CD38.
27. (Amended) The method of claim 21 [25], wherein the marker is Thy-1.
28. (Amended) The method of claim 21 [25], wherein the marker is selected from the group consisting of RT1A, RT1B, and RT1D.
29. (Amended) The method of claim 21 [25], wherein the marker is selected from the group consisting of flt-3, CD 34, c-Kit, and CD38.
37. (Amended) An isolated stem cell that does not express  $\beta_2$ -microglobulin [ $\beta_2m$ ],  
the isolated stem cell being isolated by:  
obtaining a sample of cells from a mammal;  
sorting, from the sample, cells that express  $\beta_2$ -microglobulin from cells  
that do not express  $\beta_2$ -microglobulin; and  
selecting the isolated stem cell from the sample of cells that do not  
express  $\beta_2$ -microglobulin.

Claims 6 and 7 have been cancelled.